UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,300	09/24/2004	Yung-Hi Kim	OPA9408-32/US	3662

23510 7590 10/18/2007

MICHAEL BEST & FRIEDRICH LLP
ONE SOUTH PINCKNEY STREET
P O BOX 1806
MADISON, WI 53701

EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
10/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,300	KIM ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR § 1.114

A request for continued examination under 37 CFR § 1.114, including the fee set forth in 37 CFR § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR § 1.114, and the fee set forth in 37 CFR § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR § 1.114. Applicant's submission filed on 9/10/2007 has been entered.

Status of the Claims

Applicants' amendment filed 9/10/2007 has been received and entered into the application. Accordingly, claims 30-35 have been cancelled and claims 36-38 have been added.

Applicants' arguments, filed 9/10/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Change of Examiner

The examiner assigned to the instant application has changed. The new examiner is James D. Anderson. Contact information is provided at the end of this Office Action.

Response to Amendment

Per the suggestion of the Examiner in the interview conducted 8/21/2007, Applicants have submitted new claims 36-38 drawn to the treatment of sepsis or septic shock comprising administering: (i) a lysophosphatidylcholine (LPC) represented by formula I; (ii) a sphingosylphosphorylcholine (SPC) represented by formula II; or (iii) ether derivatives of LPC represented by formula III (see claim 36). The substituents present in the LPC compounds of formulas I and III include C_{4-30} alkyl groups or alkenyl C_{4-30} groups having "one or more double bonds". The claims thus comprise the administration of thousands of different compounds to treat sepsis or septic shock. Applicants appear to have tested four specific compounds of the invention (i.e., 18:0 LPC, 14:0 LPC, 18:1 LPC, and SPC). No ether derivatives of lysophosphatidylcholine represented by formula III were tested and no LPC compounds of formula I having less than a 14 carbon alkyl group or more than one double bond were tested. However, as noted *supra*, the claims encompass treatment of sepsis or septic shock with LPC compounds having as few as four carbons as the R_1 group and any number of double bonds in the C_{4-30} alkenyl group. Whether these structurally diverse compounds will have similar activity to the tested compounds is not predictable *a priori*. Further, as will be discussed below, the activity of LPC derivatives against sepsis-induced lethality is somewhat unpredictable in that not all LPC derivatives are effective.

Accordingly, the newly submitted claims are rejected herein under 35 U.S.C 112, 1st Paragraph because, while being enabled for the treatment of sepsis and septic shock with a limited subset of the claimed compounds, the claims are not enabled for the treatment of sepsis and septic shock with the full scope of the claimed LPC derivatives.

Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-38 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the instant case, it is not clear who or what is being treated. The claims recite a method of treating sepsis or septic shock by "administering an effective amount" of a compound selected from Formula I, Formula II, or Formula III. However, to whom or what the compounds are being administered is not recited in the claims. Accordingly, the claims fail to comply with 35 U.S.C. 112, 2nd Paragraph because the population being treated has not been clearly defined.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of sepsis and septic shock with 18:0 LPC, 14:0 LPC, 18:1 LPC, and SPC, does not reasonably provide enablement for the treatment of sepsis and septic shock with the full scope of the claimed LPC derivatives. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

The nature of the invention: The invention relates to the treatment of sepsis and septic shock comprising administering: (i) a lysophosphatidylcholine (LPC) represented by formula I; (ii) a sphingosylphosphorylcholine (SPC) represented by formula II; or (iii) ether derivatives of LPC represented by formula III (see claim 36).

Relative skill of those in the art: The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

State and predictability of the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different

chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art, the examiner cites Ridermann *et al.* (Expert Opin. Biol. Ther., 2003, Vol. 3, No. 2, pages 339-350) (cited by Applicants in IDS filed 9/24/2004) and Yan *et al.* (Nature Medicine, 2004, Vol. 10, No. 2, pages 161-167) (newly cited).

Ridermann *et al.*, cited for evidentiary purposes, teaches that the history of sepsis trials has suggested that experimental models of sepsis differ significantly from human sepsis (page 346, left column) and that APC, an approved drug for treatment of patients with severe sepsis, is only clinically effective in a small amount of septic patients (*id.* at right column). Further, the authors state that "...the silver bullet for the treatment of sepsis has not yet been found" (*id.*). Further still, it appears to be important to classify the state of sepsis in a patient and to determine whether a patient has a hyper-reactive versus a hypo-reactive immune system, as the treatment strategy may depend on such immune functions (id.). Also, with regard to unpredictability, Yan *et al.*, also cited for evidentiary purposes, evaluated the therapeutic effects of lysophosphatidylcholine in experimental sepsis. In this regard, the Examiner refers to Figure 1d wherein it is apparent that not all lysophosphatidylcholines are effective in increasing the survival of mice in this model of sepsis. In fact, 6:0 LPC appears to decrease survival relative to control. 16:0 and 12:0 LPC appear to be ineffective in treating sepsis in this particular model.

In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. These articles plainly demonstrate that the art of treating sepsis, particularly in humans, is extremely unpredictable, particularly in the case of a genus of compounds being used to treat sepsis.

The breadth of the claims: The claims vary in breadth; some (such as claim 36) vary broadly, reciting the treatment of sepsis and septic shock with a broad genus of compounds. Others, such as claim 38, are narrower, reciting specific species of the claimed genus of compounds. All, however, are extremely broad insofar as they disclose the general treatment of sepsis and septic shock with the same compounds.

The amount of direction or guidance provided and the presence or absence of working examples: The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat sepsis and septic shock in all patient populations, particularly in humans, with the LPC derivatives recited in the claims. The direction concerning treating sepsis and septic shock is found in the specification at pages 19-35, which provide cellular assays and *in vivo* assays for determining the ability of the claimed compounds to treat sepsis. Four compounds of the invention were tested in these assays. Applicants describe formulations at pages 12-13. Doses required to practice their invention are described at page 13. A 10,000-fold range of doses is recommended (*e.g.*, 0.01 to 100 mg/kg), once or several times per day. Since only four lysophosphatidylcholine and sphingosylphosphorylcholine compounds as instantly claimed have

shown efficacy in treating sepsis *in vivo*, how is the skilled physician to know what dose to use for each of these structurally diverse compounds? There are both *in vitro* cellular assays and *in vivo* assays described in pages 19-35 but it is unclear if these assays correlate to the treatment of sepsis in human patients using the broad scope of compounds encompassed by the claims.

The quantity of experimentation necessary: Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of lysophosphatidylcholine derivatives could be predictably used as a treatment for sepsis and septic shock as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because four lysophosphatidylcholine derivatives have shown efficacy in an in vivo model of sepsis then all lysophosphatidylcholine derivatives must therefore, *a priori*, be useful in the treatment of sepsis and septic shock. However, the claims encompass a multitude of compounds (perhaps thousands) having chemically and biologically distinct substituents. Applicants tested four compounds with very similar substituents. For example, 18:0 LPC, 14:0 LPC, 18:1 LPC, and SPC were tested in an *in vivo* model of sepsis and were shown to increase survival. However, Yan et al. show that 12:0 and 16:0 LPC are ineffective in increasing survival in a similar model and further show that 6:0 LPC actually decreases survival relative to control. As such, the idea

that any lysophosphatidylcholine derivative having 4-30 carbons, optionally having one or more double bonds, will be an effective treatment for sepsis appears to be purely an invitation to experiment to determine exactly what compounds of the invention will have the claimed activity.

Determining if any particular claimed compound would treat sepsis or septic shock would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the guidance and direction provided by Applicants. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Allowable Subject Matter

Favorable consideration would be given to claims limited to the treatment of sepsis and septic shock with 18:0 LPC, 14:0 LPC, 18:1 LPC, or SPC.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

October 11, 2007

10/13/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER